U.S.C. 112, first paragraph and on 35 U.S.C. 102 and 103 based on Garcia as the primary reference.

Rejection under 35 U.S. C. § 103

1. Claims 1-10, 16-22 and 38

Claims 1-10, 16-22 and 38 are alleged to be obvious over Carney *et al.* ("Carney") in view of Garcia *et al.* ("Garcia"). The Examiner alleges that Carney teaches disseminated small cell lung cancer human tumor cell lines that are derived from bone marrow and pleural exudate. The Examiner states that Carney does not teach that the cell has integrated in its genome or another replicative genetic element the DNA encoding at least on immortalizing oncogene into a non-immortilized epithelial cell. Further, the Examiner states that Carney does not teach at least one defect in the origin of replication or in the *in vitro* process by which the tumor cell incorporates the DNA encoding at least one immortalizing oncocgene into a non-immortalized epithelial tumor cell. The Examiner additionally states that Carney lacks the method step of incorporating DNA via microinjection, which is performed after the step of carrying out a primary expansion of the epithelial tumor cells comprising the step of culturing in a medium with epidermal growth factor on the extracellular matrix, collagen coated tissue flasks. To correct the defects of Carney, the Examiner alleges that Garcia teaches an autologous, disseminated immortalized rabbit mammary epithelial tumor cells which has integrated in its genome or another contains the large T antigen of non-infectious SV40 DNA and which contains at least one defect in the origin of replication. The Examiner further alleges that Garcia teaches an epithelial tumor cell that has integrated in its genome at least one additional oncogene, wherein the additional oncogene is c-Ha-ras. The Examiner maintains that Garcia teaches the *in vitro* process by which the tumor cell incorporated the DNA encoding at least one immortalizing oncogene. The Examiner alleges that the incorporation step comprises microinjection, which was performed after the step of carrying out a primary expansion of the epithelial tumors cells. The Examiner states that the primary expansion comprises the step of culturing in a medium that comprises epidermal growth factor on the extracellular matrix, collagen coated tissue flasks.

The Examiner then concludes that based upon the teachings of Carney and Garcia that it would have been obvious to use the cell line of Carney to establish a metastatic cell

line suitable for studying the immortalizing and transforming potential of known and candidate genes for epithelial cells motivated by Carney and Garcia that the establishment of such a cell line could be readily made and successfully propagated in order to conduct experiments for the long term study of metastasis

Applicants respectfully traverse this rejection because the Examiner has used applicants' own disclosure and impermissible hindsight to combine Carney and Garcia to arrive at the claimed invention. However, in an effort to expedite prosecution, claim 1 has been amended to recite that the claimed cells are immortalized, non-small cell lung cancer (non-SCLC) epithelial tumor cells with metastatic potential.

The present invention provides immortalized non-SCLC epithelial tumor cells that are derived from the earliest metastasizing cells which have conserved the phenotype of the residual tumor cells present in the patient. See the paragraph bridging pages 4 and 5 of the specification. It is important to recognize these cells at this very early stage and generate quantities of them to analyze the early stages of cancer for identification and therapeutic methods.

Carney allegedly discloses disseminated small cell lung cancer (SCLC) human tumor cell lines that are derived from bone marrow and pleural exudate. Independent claim 1 is now directed to non-SCLC cells, which Carney does not disclose. Applicants believe that Carney is no longer a viable reference to form the basis of this rejection. Further, it does not appear that persons skilled in the art would not be able to distinguish SCLC cells from non-SCLC cells because as early as the mid-1980's by persons skilled in the art knew that SCLC and non-SCLC cells were different and distinguishable on the basis of the presence of specific marker or amounts of these markers in these cells. In support of this statement, applicants enclose a table, as Appendix A, that summarizes the research of several scientists, who investigated the presence of markers on SCLC ,non-SCLC and/or other lung cancer cells. Of particular interest is Bepler *et al.* (copy enclosed as Appendix B) that shows that CK-BB (BB isoenzyme of creatine kinase) and CEA are specific markers for SCLC.

In addition to the above arguments, applicants believe that the obviousness rejection based on Carney in view of Garcia is improper. Carney discloses on page 2915, first column, first complete paragraph, that "[n]o cell lines were established from specimens pathologically and cytologically negative for SCLC tumor cells (Table 2)." See Table 2

which shows that no cell lines were established for 184 bone marrow specimens that were SCLC negative, whereas cell lines were established from 12 of the 16 SCLC positive cells of the 200 tested bone marrow specimens. Thus, a skilled person in the art takes from Carney that tumor negative cells cannot be used to establish cell lines where as tumor positive cells can be used to establish cell lines.

In contrast, the present invention discloses on page 28, Example 8, that cell lines were established from early disseminated cells in the bone marrow that would have been classified as tumor-free by conventional detection methods as used by Carney.

The Examiner suggests that to obtain the "immortalized epithelial tumor cell with metastatic potential" of the present invention, a skilled person would be motivated to utilize the methods of Garcia to establish a cell line. The specification defines "metastatic potential" as "the potential of said epithelial tumor cell to be the nucleus of metastatic formation." As argued in previous responses, Garcia does not disclose the transformation of a tumor cell but rather Garcia describes the transformation of a normal epithelial cell, and therefore the immortalization of a non-tumor cell. Furthermore, Garcia discloses the transformation of a rabbit cell by micro-injecting SV40 viral DNA and/or the human oncogene Ha-ras. In this regard, Garcia stresses on page 1980, left-hand column, first paragraph of discussion, second and third paragraphs:

> "When injected alone, these molecules were unable to transform rabbit mammary cells. The combination of SV40 DNA and activated c-Ha-ras gene, however, induced drastic changes in the micro-injected cells" (emphasis added)

In addition, on page 1974, right-hand column, last sentence of the introduction, Garcia points out:

> "An immortalized cell line obtained after injecting SV40 DNA into primary cells retained some but not all of the differentiation markers of mammary secretory cells from pregnant rabbits, whereas a cell line fully transformed by SV40 and the activated human c-Ha-ras DNA became tumorigenic." (emphasis added)

Therefore, Garcia teaches that tumorigenic cells can be obtained form normal epithelial cells by co-injecting SV40 and the human oncogene c-Ha-ras.

Further, there is simply no motivation to utilize the method of Garcia to make metastatic cell lines of Carney's cells. Table 2 of Carney shows that SCLC negative cells

cannot be used to establish cell lines and 75% of the SCLC positive cells are used to establish cell lines, showing that SCLC positive cells do not need Garcia's methods to establish cell lines.

Applicants respectfully disagree with the Examiner's rationale for combining the cited prior art and for utilizing impermissible hindsight to construct the present rejection based upon Applicants' own disclosure. When combining elements to make out a *prima facie* case of obviousness, the Examiner is obliged to show by reference to specific evidence in the cited references that there was (i) a suggestion to make the combination and (ii) a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The Examiner has failed to support the alleged case of *prima facie* obviousness.

Obviousness "'cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.'" *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988), *citing ACS Hosp. Sys. v. Montefiore Hosp.*, 221 USPQ 929, 933 (Fed. Cir. 1984). It is applicants' position that the combination of the prior art fails to provide a suggestion to make the present invention. For this reason and all of the arguments presented above, this rejection should be withdrawn in regard to the rejected claims.

2. Claims 1-12, 16-22, 31 and 38

Claims 1-12, 16-22, 31 and 38 are alleged to be obvious over Carney *et al.* ("Carney") in view of Garcia *et al.* ("Garcia") and Blankenstein *et al.* ("Blankenstein"). The Examiner applies Carney and Garcia as above and Blankenstein to teach the transfer of single cytokine genes into cancer cells. The addition of Blankenstein fails to cure the deficiencies in the primary references, and in view of the above arguments directed to the combination of the primary references, it is requested that this rejection be withdrawn.

3. Claims 1-10, 16-22, 31 and 38

Claims 1-10, 16-22, 31 and 38 are alleged to be obvious over Carney *et al.* ("Carney") in view of Garcia *et al.* ("Garcia") and the Sigma Cell Cutlure Catalogue and

Price List ("Sigma"). The Examiner applies Carney and Garcia as above and Sigma to teach to availability of growth factor supplements for use in the culture medium. The addition of Sigma fails to cure the deficiencies in the primary references, and in view of the all of the above arguments directed to the combination of the primary references, it is requested that this rejection be withdrawn.

4. Claims 1-10, 16-22, 33, 34 and 38

Claims 1-10, 16-22, 33, 34 and 38 are alleged to be obvious over Carney *et al.* ("Carney") in view of Garcia *et al.* ("Garcia") and Gottlinger *et al.* ("Gottlinger"). The Examiner applies Carney and Garcia as above and Gottlinger to teach to epithelial surface antigens and adjuvants suitable for mounting an immunological response. The addition of Gottliner fails to cure the deficiencies in the primary references, and in view of the all of the above arguments, it is requested that this rejection be withdrawn.

## CONCLUSION

Applicants kindly request consideration of the amendment of claim 1 and arguments presented herein. Applicants submit that this application is in condition for allowance, and they solicit an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned, at the telephone number listed below, is courteously invited.

Respectfully submitted,

August 13, 2001
Date

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**MARK-UP CLAIMS**

1. (Twice amended) An immortalized, non-small cell lung cancer, epithelial tumor cell with metastatic potential which has integrated in its genome or another replicative genetic element an externally introduced immortalizing oncogene which is expressed in said cell.